REMARKS/ARGUMENTS

Applicants thank Examiner Robinson and Supervisory Examiner Weber for the courtesies shown in a telephonic interview on October 12, 2007. The Examiner's Interview Summary has been received. As noted in the Summary, the Office indicated during the interview that claims submitted for discussion would not raise an issue under 35 USC 112, first paragraph. These claims are added herewith as new claims 91-93. New claims 94 and 95 are the same as claims 91 and 93, respectively, except that they recite "5 kilobasepairs" rather than "10 kilobasepairs." Support is found in the specification at, for example, paragraphs [0121]-[0122].

Claims 1, 75, 85, 86, 88 and 90 are amended and are now directed to synthetic genes encoding a polyketide synthase protein. Claims 2 is cancelled. Claims 16, 44 and 51, which were withdrawn, are cancelled. Amendment and cacellation of claims is without prejudice to furure prosecution of the original subject matter in this or a related application. Following entry of this amendment claims 1, 3-16, and 69-95 will be pending.

Specification Objection

The Office objected to the specification for not supporting "less than about 90%" which was found in the original claims. However, this phrase is supported in the specification. See, e.g., paragraphs [0010] and [0277].

Rejections Under 35 USC 112, First Paragraph

As noted above, the Office has indicated that (at least) new claims 91-93 are supported and enabled by the specification. Applicants respectfully submit that, for the same reasons, all of the claims currently pending are in compliance with 35 USC 112, first paragraph. For completeness of the record Applicants reiterate the remarks presented in the response filed Feb. 27, 2007. These remarks are provided below. (Because Applicants believe agreement has been reached on this issue, citations to specific claims have not been changed to conform to amendments and cancellations in the instant amendment.)

Written Description

Claims 1-15 and 69-90 were alleged not to be described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The inventors have disclosed a new method for making synthetic genes and has described novel synthetic genes made by this process. Using this method very large synthetic genes (e.g., > 20 kb) can be synthesized very rapidly, economically and accurately. A unique, identifying feature of the synthetic genes is that they can encode the amino acid sequence identical to that of a naturally occurring protein (e.g., myosin) but have a nucleotide sequence that differs dramatically from the naturally occurring gene (e.g., myosin gene). The synthetic methods disclosed by the instant inventors may be used to engineer very large synthetic genes with a variety of useful properties without undesirably changing the encoded protein.

Using this method, synthetic genes for essentially any naturally occuring polypeptide can be synthesized, having the unique features that distinguish it from genes found in nature. Indeed, the inventors described more than 85 kilobases of synthetic sequences. One of ordinary skill in the art reading the specification would immediately recognize this and understand that the inventors evidenced "possession" of the synthetic method and its products.

The Office has rejected claim 1 and other claims as allegedly not described in the specification. In articulating this rejection for written description the Office makes a number of arguments. The relevance of some of these arguments to the present invention is not clear. For example, the Office asserts that "the genus of claimed polypeptides encompasses widely variant species" and that "based on unlimited variations . . . one of skill would at best expect a protein that is different or at worst a protein that is not functional." As the instant claims are not directed to polypeptides this rejection is confusing. In this response Applicants endevor to address the concerns of the Office as completely as possible. Applicants reiterate their previously made

offer and request for a telephonic interview to explain aspects of the invention and to better address any concerns of the Office.

As Applicants understand it, the core of the concerns articulated by the Office are that claims that recite the term "polypeptide segment" (e.g., claim 1[1]) do not recite a *particular* polypeptide segment. The Office states that the claims encompass a large variable genus and asserts the skilled artisan cannot envision the detailed chemical structure of the genus encompassed. The Office also states "the specification fails to provide any additional representative species of the claimed genus to show that the application was in possession of the claimed genus." As noted above, the specification provides >85 kilobases of synthetic genes falling within the scope of the claims. It would be clear to one of skill in the art, with undergraduate knowledge of the genetic code and the relationship between DNA and amino acid sequences, and guided by the teachings of the specification providing detailed description of the design of synthetic genes that the inventors had possession of the invention claimed. The Office is respectfully asked to explain what purpose would be served by provision of an additional 85, or 100, or 1000 kilobases of synthetic genes.

As noted, the present inventors have disclosed a new method for making synthetic genes encoding naturally occuring protein sequences, and synthetic genes made by this method. The synthetic genes have identifying structural features which are recited in the claims such as, *inter alia*, a low level of sequence identity with naturally occurring counterparts.

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1 Claim 1 [as pending following entry of the amendment of Feb. 27, 2007] read: A synthetic gene encoding a polypeptide segment, wherein said polypeptide segment corresponds to a reference polypeptide segment encoded by a naturally occurring gene, and

a) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are the same length and comprise at least 50 amino acids;

b) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are at least 95% identical in amino acid sequence; and

c) the polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoding sequence of the naturally occurring gene is are less than 90% identical in nucleotide sequence.

The present specification teaches that the sequences of naturally occurring genes are known (for example, referencing GenBank, *see* paragraphs [0178] and [0352]). For illustration the specification provides numerous accession numbers from which one of skill can readily find protein sequences and corresponding gene sequences. Moreover, the specification provides a detailed description of several synthetic genes made according to the invention (see, e.g., Examples 7 and 9 and Tables 14A-B and 17A). These synthetic genes encoding nine large polypeptides (ranging from about 1,410 amino acids to >7,000 amino acids in length) with > 99.7 % sequence identity with the corresponding naturally occurring polypeptide but only 74-76% sequence identity with the naturally occurring gene.

The Office states "the specification fails to provide any additional representative species of the claimed genus to show that the application was in possession of the claimed genus." The Office appears to believe the written description requirement requires that the specification provide examples of an unspecified ("representative") additional number of naturally occuring polypeptides or genes. This is not a requirement of Section 112. In their decision in *Falkner v. Inglis* the Court of Appeals for the Federal Circuit stated:

> "a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention."[2]

The *Falkner* Court continued

> "Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences . . . satisfaction of the written

[2] Falkner v. Inglis (Fed Cir 2006) 79 USPQ2d 1001; 448 F3d 1357.

description requirement does not require either the recitation or incorporation by reference."[3]

In *Falkner* an interference count was directed to vaccines comprising a poxvirus vector having a deleted or inactivated essential gene. Appellants argued that the Patentees had not described and enabled vaccines comprising a poxvirus vector having a deleted or inactivated essential gene because the patent did not identify *any* essential poxvirus genes or the inactivation of any such genes. In response, the Court held neither examples nor actual reduction to practice nor recitation of known structures nor incorporation by reference of literature describing known structures was required to comply with Section 112.

In another case, *Capon v. Eshhar*,[4] the Federal Circuit faced a similar issue and similarly ruled that written description does not require recitation of known sequences. In *Capon* claims were directed to chimeric DNA encoding single-chain chimeric proteins for expression on the surface of cells of the immune system. The chimeric DNA combined a first segment encoding all or a portion of a protein "expressed on the surface of cells of the immune system" (e.g., a lymphocyte signaling protein) and a second segment encoding the single-chain variable ("scFv") domain of "a specific antibody" (e.g., unspecified antibodies against "tumor cells," "virus infected cells," and the like).[5] The Board of Patent Appeals and Interferences held that neither party described "by reference to contemporary and/or prior knowledge in the art of the structure, formula, chemical name, or physical properties of many protein domains, and/or DNA sequences

[3] Falkner v. Inglis (Fed Cir 2006) 79 USPQ2d 1001; 448 F3d 1357.
[4] Capon v. Eshhar 76 USPQ2d 1078 (Fed. Cir. 2005).
[5] Claim 1 of application No. 08/084,994 to Eshhar et al. is described. The claim reads:
1. A chimeric gene comprising a first gene segment encoding a single-chain Fv domain (scFv) of a specific antibody and a second gene segment encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein wherein said endogenous protein is expressed on the surface of cells of the immune system and triggers activation and/or proliferation of said cells, which chimeric gene, upon transfection to said cells of the immune system, expresses said scFv domain and said domains of said endogenous protein in one single chain on the surface of the transfected cells such that the transfected cells are triggered to activate and/or proliferate and have MHC nonrestricted antibody-type specificity when said expressed scFV domain binds to its antigen.

which encode many protein domains" and that neither application in interference was in compliance with the written description requirement.

The *Capon* Court vacated the decision of the Board and held:

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.[6]

As in *Capon*, the present invention is not the discovery of naturally occurring genes, and recitation of specific gene sequences in the claims is neither necessary nor appropriate. Accessible literature sources, including Genbank, clearly provided, as of the relevant date, genes and their nucleotide sequences. Moreover, several exemplary large genes were described in detail. Applicants respectfully submit that any individual skilled in the art would recognize that Applicants had possession of the claimed invention.

Enablement

The rejection articulated by the Office in rejecting the claims as allegedly not enabled mirrors the rejection for alleged lack of description. The Office asserts that the "amount of experimentation required to practice the claimed invention is undue as the claims encompass a large variable genus of polypeptide segments and nucleic acid segments encoding said

[6] Capon v. Eshhar

polypeptide" and that a "large quantity of experimentation [would be] necessary to generate the infinite number of variants/fragments recited in the claims and possibly screen same for activity . . ." First, Applicants respectfully submit that clearly it is impossible to make an "infinite" number of species, with or without experimentation, and that enablement does not require that every species encompassed in a claim be made.[7] What is more relevant is that the Office has not provided a single example of a synthetic gene of the invention that would require undue experimentation to make. On the contrary, the specification provides a detailed description of how to make and use the claimed synthetic genes. The enabling disclosure provides working examples of *more than 85 kb* of synthetic genes. Applicants respectfully submit that one of ordinary skill in the art (who would of course have knowledge of the genetic code and the basic principles of molecular biology) would find that the specification is enabling.

The Office also discusses at considerable length whether potential changes in a protein's amino acid sequence could be "tolerated" (by which the Office means, would not be deleterious to the activity of a protein). As an initial matter, the claims are not directed to a protein, let alone a protein with a specified activity, nor is the claim directed to the discovery of a new protein structure.[8] It should be clear that the invention is directed to *synthetic genes* that encode a polypeptide segment that has substantial (e.g., 95% - 100%) identity to a naturally occurring protein segment. Even if, *arguendo*, an occational polypeptide does not retain the biological activity of the naturally occurring counterpart, this is irrelevant to the question of whether the teachings of the specification enable one of skill to make and use the claimed synthetic gene. Moreover, the person of skill has complete control over the polypeptide sequences encoded in the synthetic gene. Any "change" in a protein's amino acid sequence would be a change predicted, desired and intended by the person of skill practicing the invention.

[7] Applicants also note that virtually any claim with "comprising" language could be said to encompass an infinite number of species.
[8] The Office appears to have confused the gene sequence and the polypeptide sequence (see Office Action, page 9, line 12 - page 12, line 7).

Rejections Under 35 USC 112, Second Paragraph

Claims 1, 75, 85-86, 88, and 90 were rejected as indefinite because "no structure is recited in the claims." Applicants believe this issue is fully addresses in the discussion above concerning the first paragraph of Section 112. Should the Examiner have any questions she is invited to contact the undersigned.

Conclusion

For the reasons provided above, Applicants respectfully request that the claims now pending be examined and a Notice of Allowance issued.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

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Respectfully submitted,

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